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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/598,982	MAFFITT ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25, 34-37, 41-45, 54-58, 62-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9-16,19-25,34-37,41 and 42* is/are rejected.

7)☒ Claim(s) *7,8,17,18,43-45,54-58,62 and 63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-25, 34-37, 41-45, 54-58, 62-63 are pending.

Applicant's amendment of claims 1, 5, 6, 41, addition of claims 62-63, cancellation of claims 26-33, 38-40, 46-53, 59-61, amendments to the specification, and submission of new drawings, in a communication filed on 7/22/2003 are acknowledged.

Applicant's submission of a new sequence listing in electronic and paper form, in a communication filed on 10/16/2003 is acknowledged.

Applicants submit that in regard to the previous supplemental restriction requirement, Applicants interpreted the requirement as being an election of species since it was indicated that Group I was generic. Applicants traverse the supplemental restriction requirement citing MPEP 2434. In particular, Applicants submit that all the species recited are extremely similar in structure and it would not impose a serious burden to search all the species recited.

Applicant's arguments have been fully considered. Upon further consideration, the previous supplemental restriction requirement is withdrawn in view of the fact that an alignment of the polynucleotides of SEQ ID NO: 8, 20, 22, 24, 26, 36, 38, 40, 42, and an alignment of the polypeptides SEQ ID NO: 9, 21, 23, 25, 27, 37, 39, 41 and 43 show that the polynucleotide of SEQ ID NO: 20 and the other polynucleotides recited are identical except for 14 mismatches and the polypeptide of SEQ ID NO: 21 and the other polypeptides recited are identical except for 4 mismatches. Since a search of the polynucleotide SEQ ID NO: 20 and a polynucleotide encoding the polypeptide of SEQ ID NO: 21 has already being conducted, this search is deemed co-extensive in regard to the other highly structurally homologous species recited.

Claims 43-45 and 54-58 previously withdrawn from further consideration are now rejoined for examination on the merits. New claims 62-63 are drawn to the elected invention and

are being examined herein. Claims 1-25, 34-37, 41-45, 54-58, 62-63 are now under consideration.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 120 or 121 to US application No. 09/079,970 filed on 05/15/1998.

Terminal Disclaimer

2. The terminal disclaimer filed on 7/22/2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6274366 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Drawings

3. The drawings submitted on 7/22/2003 are accepted by the Examiner.

Claim Objections

4. Claims 7 and 17 are objected to due to the recitation of "wherein the DNA sequence....has a DNA sequence selected from the group....". For clarity and consistency, it is suggested that the term be amended to recite "wherein the DNA sequence....is a DNA sequence selected from the group....". Appropriate correction is required.

5. Claims 34-37 and 56-58 are objected to due to the recitation in claims 34, 37 and 56 of "a genetically-engineered eukaryotic cell ....comprising a eukaryotic host cell transformed..". For

clarity, it is suggested that the term be amended to recite "a genetically-engineered eukaryotic cell...wherein said eukaryotic cell is transformed ....". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-6, 9-12, 20-25, 34-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 (claims 2-6, 9-12, 34-36 dependent thereon) is indefinite in the recitation of "proteolytic tryptase having an active site mutation at an amino acid position selected from positions 44, 91 and 194 of the proteolytic tryptase" because it is unclear which position is being referred to without indicating the specific sequence associated with positions 44, 91 and 194. Since the claim reads on any proteolytic tryptase (from any species), there is no specific sequence associated with positions 44, 91, and 194. It is suggested that applicants amend the claim to include a numerical sequence identifier (SEQ ID NO: #) if the intended sequence has been disclosed in the sequence listing or to clearly identify the sequence associated with positions 44, 91, and 194. For examination purposes, no patentable weight will be given to the term. Correction is required.

9. Claims 2 and 3 are indefinite in the recitation of "β-I tryptase" or "β-II tryptase" as it is unclear which β-tryptases are encompassed by the claims. While the art recognizes at least two groups of tryptases, α and β, there is no teaching as to what are the functional and structural characteristics which differentiate a "β-I tryptase" from a "β-II tryptase", such that one of skill in the art would readily recognize whether a polypeptide is a "β-I tryptase" or a "β-II tryptase". For

examination purposes, the terms will be assumed to recite "β-tryptase". Thus, claims 2 and 3 will be considered duplicates. Correction is required.

10. Claim 20 (claims 21-25 dependent thereon) is indefinite in the recitation of "a method of producing an active site mutation of proteolytic tryptases comprising transforming a eukaryotic host cell ....., wherein the ...host cell expresses enzymatically active ...tryptase" for the following reasons. While the preamble refers to the claimed method as one for producing an active site mutation, the steps in the method are those for producing an inactive tryptase. For examination purposes, it will be assumed that the claim is directed to a method of producing an inactive proteolytic tryptase. Correction is required.

11. Applicants are advised that if amendments to the claims are made, dependent claims may have to be further amended for clarity and/or appropriate antecedent basis.

Claim Rejections - 35 USC § 112, First Paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-6, 9-16, 19-25, 34-37, 41-42 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in previous Office Action Paper No. 12.

14. Applicants argue that claim 1 has been amended to refer to specific positions where the mutation is to appear. Applicants also submit that they are not required to define all attributes of all species falling within the genus to satisfy the written description requirement. Applicants

argue that how a teaching is provided is not dictated by statutes, regulations, case law or the MPEP. According to Applicants, a listing of exemplary species and/or the use of broader terminology are valid and approved approaches to defining a generic term. Applicants assert that they are not required to disclose even a single species. Applicants refer to Exhibit A in support of the argument that tryptases are art-recognized enzymes that catalyze the same core chemical transformation. Also, Applicants submit that they are not claiming all DNA constructs but rather those which encode a defined polypeptide. It is Applicant's contention that tryptases having an active site mutation is novel and that the specification provides both by working examples and broad terminology, how to obtain a gene encoding a tryptase, how and where to mutate the gene, how to make a construct which can be expressed, and how to isolate the desired tryptase.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the amendments made to claim 1. However, as explained above, a recitation of specific amino acid positions without indicating the sequences to which those positions correspond is indefinite and has been given no patentable weight. See discussion above. Claims 1-6, 9-16, 19-25, 34-37, and 41-42 are directed to DNA constructs comprising a genus of polynucleotides encoding any inactive or active proteolytic tryptase, β-tryptase or human proteolytic tryptase, eukaryotic host cells comprising said DNA constructs, or methods to recombinantly produce the polypeptides encoded by said DNA constructs. While it is agreed that (1) tryptases are art-recognized enzymes, (2) not all species in a genus have to be disclosed, and (3) the specification provides some working examples, the Examiner disagrees with Applicant's contention that, in the instant case, not even a single species has to be disclosed, or that the teachings of the specification or the art provide adequate description of any active/inactive proteolytic tryptase, β-tryptase or human proteolytic tryptase as recited in the claims.

While a sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleic acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus., in the instant case, there is no structural feature which is representative of all the members of the genus of polynucleotides encoding any active/inactive proteolytic tryptase, β-tryptase or human proteolytic tryptase as recited in the claims. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. As clearly stated in the previous Office Action, while the argument can be made that the species in the claimed genus are adequately described since they can be isolated by using structural homology with structures disclosed in the prior art or the specification, the art shows that isolation of such species is unpredictable since even when there is high structural similarity, function may be different. See particularly the teachings of Witkowski et al., Broun et al. and Seffernick et al. already discussed. The genus of polynucleotides required in the DNA constructs encompass a structurally diverse group which can not be adequately described by the few species known in the art or those described in the specification. Thus, one cannot reasonably conclude that the claimed invention meets the written description requirement under 35 USC 112, first paragraph.

16. Claims 1-6, 9-16, 19-25, 34-37, 41-42 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (a) a DNA construct comprising polynucleotides encoding the polypeptides of SEQ ID NO: 9, 21, 23, 25, 27, 37, 39, 41, and 43, (b) eukaryotic host cells comprising the DNA construct of (a), and (c) a method of producing the polypeptides of SEQ ID NO: 9, 21, 23, 25, 27, 37, 39, 41, and 43 by cultivating a eukaryotic host cell transformed with the DNA construct of (a), does not reasonably provide enablement for (1) a DNA construct comprising polynucleotides encoding any active or inactive proteolytic tryptase, β-tryptase, or human proteolytic tryptase, (2) eukaryotic host cells comprising the DNA constructs of (1), or (3) a method to recombinantly produce any active or inactive proteolytic tryptase, β-tryptase, or human proteolytic tryptase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in previous Office Action Paper No. 12.

17. Applicants argue that this rejection has been overcome by amendments to the claims, specifically that made to claim 1. Applicants incorporate the arguments presented above in regard to the written description rejection. According to Applicants, the Office fails to articulate why the disclosure falls short and is requiring a certain base line number of working examples to enable the claims. Applicants indicate that satisfaction of the enablement requirement is not voided by the need of some experimentation such as routine screening. Applicants submit that the specification provides a wealth of guidance on how to make the claimed constructs, how to transform host cells, how to isolate the enzyme encoded by the DNA constructs and how to characterize the enzyme isolated.

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. As indicated above, while the Examiner acknowledges the amendments made to claim 1, the positions recited are indefinite absent a specific sequence associated with

those positions. See discussion above for the Examiner's position addressing the arguments presented regarding the written description rejection. With respect to Applicant's arguments that the Office requires a base line number of working examples to enable the claims, and that routine experimentation does not preclude enablement, the Examiner is not contenting that Applicants must disclose working examples or that the need for routine experimentation renders an invention not enabled. As indicated previously, the instant claims were rejected and remain rejected in view of the fact that undue experimentation is required in order to enable the full scope of the claims. While the claims require a polynucleotide encoding any active/inactive proteolytic tryptase, human proteolytic tryptase, or β-tryptase, neither the specification nor the art provide the amount of guidance or direction required for one of skill in the art to isolate those polynucleotides required in the DNA constructs. The Examiner acknowledges the teachings of the specification and the fact that some of the polynucleotides encompassed by the claims are known. However, the claims not only encompass what is already known in the art or disclosed by Applicants, but they require any polynucleotide encoding any active/inactive proteolytic tryptase, human proteolytic tryptase, or β-tryptase. As such, the claims require polynucleotides which are unknown. As discussed in the previous Office Action, isolation of unknown polynucleotides encoding polypeptides having the desired function is not routine experimentation since the art clearly teaches the unpredictability of isolating species having the desired function based solely on structural homology. See particularly the teachings of Witkowski et al., Seffernick et al. and Broun et al. already discussed, where examples are shown of how even highly structurally homologous polypeptides did not share the same function. It is reiterated herein that structure determines function, therefore one of skill in the art would require some knowledge or guidance as to which are the structural elements required in any polynucleotide such that they encode any active/inactive proteolytic tryptase, human proteolytic tryptase, or β-tryptase.

While it is agreed that the teachings of the specification regarding the mutations in the active site of one human proteolytic tryptase provide additional information further characterizing the human proteolytic tryptase, it is unclear as to whether (a) all proteolytic tryptases, β-tryptases, or human tryptases will have the same structural characteristics at the active site as those of the human proteolytic tryptase disclosed in the instant application, and (2) the mutations made to the active site of a single human proteolytic tryptase can be made to any proteolytic tryptase, human proteolytic tryptase or any β-tryptase (from any source) to inactivate them even if the active site's structural characteristics of these tryptases are different from those of the active site of the human proteolytic tryptase disclosed. Testing an infinite number of polynucleotides to determine which ones encode polypeptides with the desired activity, determining the active site of those which have the desired activity, and determine the mutations which would render the polypeptide inactive would constitute undue experimentation. Therefore, in view of the information provided and the unpredictability of the art, one cannot reasonably conclude that the teachings of the specification or the prior art enable the full scope of the claimed invention.

Double Patenting

19. Claims 41-42 were rejected under the judicially created doctrine of double patenting over claims 1-7 of U.S. Patent No. 6274366.

20. In view of Applicant's submission of a terminal disclaimer on 7/22/2003 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent No. 6274366, this rejection is hereby withdrawn.

Allowable Subject Matter

21. Claims 7-8, 17-18, 43-45, 54-58, 62 and 63 appear to be allowable over the prior art of record but are objected to since they depend upon a base rejected claim.

Conclusion

22. No claim is in condition for allowance.

23. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
September 16, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600